Endocrine Journal 2002, **49** (3), 307–314

Is Antithyroid Treatment Really Relevant for Young Patients with Subclinical Hyperthyroidism?

ÖZLEM YÖNEM, HATICE SEBILA DÖKMETAŞ*, SÜLEYMAN MURAT ASLAN** AND TANER ERSELCAN***

Department of Internal Medicine, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey
**Department of Endocrinology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*
***Department of Cardiology, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*
****Department of Nuclear Medicine, Faculty of Medicine, Cumhuriyet University, Sivas, Turkey*

Abstract. This study investigated whether symptoms and findings of hyperthyroidism exist in patients with subclinical hyperthyroidism (SCH) and sought to determine whether hyperthyroidism treatment improves them. Twenty patients (mean age: 36.10 ± 1.41 years) and 20 healthy controls [mean age: 36.35 ± 1.50 years) were included in the study. The SCH duration of patients was at least 6 months. Bone mineral density (BMD) was measured in both patients and controls. The patients were randomly divided into 2 groups of 10 patients each. Symptoms and findings of hyperthyroidism were evaluated and BMD, 24 hour ambulatory blood pressure, holter measurements and serum lipids were determined initially in both groups and 6 months after the attainment of euthyroidism in the treatment group (Group 1) and after a 6 month follow-up in the observation group (Group 2). In the patient group, BMD showed a decrease of 1.3% and 3.9% in femur neck and L_{1-4} vertebra compared with controls, respectively. But there was no difference in BMD between patients and controls. Fatigue, nervousness, over sweating, tachycardia and tremor improved with treatment. The number of patients with fatigue, nervousness, over sweating and tachycardia increased in Group 2 after the observation. There was no difference between initial values and after a 6 month period from observation or on attainment of euthyroidism in the values of BMD, lipids, minimal and maximal heart rate, total number of ventricular and supraventricular beats and heart rate variability. As a result symptoms of hyperthyroidism were found to be increased in SCH but they partly decreased after antithyroid treatment. But no favourable effects of antithyroid treatment on BMD, heart rate and arrhythmia incidence were found in young, premenopausal patients with SCH during the 6 month period.

Key words: Subclinical hyperthyroidism, Antithyroid treatment, BMD, Heart rate variability, Blood pressure
(*Endocrine Journal* **49**: 307–314, 2002)

SUBCLINICAL hyperthyroidism (SCH) includes conditions in which serum thyrotropin (TSH) is suppressed while serum thyroxine (T4) and triiodothyronine (T3) levels remain normal [1]. The prevalence of SCH in the population varies from 2–16% [2]. Progression of SCH to overt thyrotoxicosis is rare and this ratio was reported to be 4% or less per year in autonomous thyroid nodules [3].

Received: October 25, 2001
Accepted: February 4, 2002
Correspondence to: Dr. Hatice Sebila DOKMETAS, Cumhuriyet Üniversitesi Tıp Fakültesi, Endokrinoloji ve Metabolizma Bilim Dalı, 58140, Sivas, Turkey

The most important morbidity and mortality causing effects of overt thyrotoxicosis are seen in cardiovascular and musculoskeletal systems. In the heart, while heart rate and systolic arterial tension increase by its effect on the sympathetic nervous system, diastolic dysfunction leads to myocardial hypertrophy increasing the vulnerability to atrial arrhythmia [3]. In many recent studies the effects of hyperthyroidism on skeletal system have been investigated. Hyperthyroidism has been thought to increase the bone turnover and shorten the normal remodelling cycle of bone [4]. It is not clear whether the changes in overt hyperthyroidism also exist in SCH or not.

The role of antithyroid treatment in SCH is dis-

cussed. While some authors suggest only observation, others advise treatment in the presence of atrial fibrillation and osteoporosis [1]. The purpose of this study is to firstly determine which of the symptoms and findings of hyperthyroidism exist in SCH and then to find out whether treatment improves the symptoms and findings of hyperthyroidism by a prospective randomised controlled study.

Patients and Methods

Patients

Nineteen premenopausal women and 1 man having SCH duration of at least 6 months, with an age range 24–48 years (mean: 36.10 ± 1.41 years), and 19 premenopausal women and 1 man healthy controls having an age range of 24–50 years (mean: 36.35 ± 1.50 years) were included in this study. The SCH duration of patients varied between 6–60 months (mean: 15.85 ± 3.16 months). Serum parathyroid hormone levels, together with liver and kidney function tests of both patients and controls were normal, each of the premenopausal women had regular menstrual cycles and none of the patients or control cases had diabetes mellitus, pituitary, psychiatric or other acute or chronic systemic disease. None of the patients used L-thyroxine or antithyroid drug for hyperthyroidism treatment, β-blocking agent, or drugs related to the aetiology or treatment of osteoporosis. When choosing the control group, matching the parameters such as age and sex with the control group was taken into consideration.

Study protocol

The local ethics committee approved the study and written consent was obtained from all patients after giving them information about the study. Bone mineral density (BMD) of femur neck (BMDF) and L_{1-4} lumbar vertebra (BMDL) was measured in both patients and controls. Data on smoking, alcohol, exercise, and milk-drinking habits were obtained in both groups. The patients were examined by using a scale involving hyperthyroidism symptoms, and the findings were derived from the studies of Davis and Trivelle [5, 6]. A total of 20 patients were randomly divided into two groups. Ten patients in group 1, with 2 of them being subclinical hyperthyroidic patients with Graves' disease who had not experienced overt thyrotoxicosis yet, and 8 patients with autonomous nodule received antithyroid treatment (9 patients propylthiouracil, 3 × 50 mg/day, 1 patient radioactive iodine) while the other 10 patients in group 2 were observed without any treatment. Euthyroidism was attained in the treatment group after three months. None of the patients became euthyroid during the observation period. Triglyceride, cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), sex hormone binding globulin (SHBG), BMD, ambulatory systolic (SBP) and diastolic blood pressure (DBP) and holter measurements were determined initially in both groups, and 6 months after the attainment of euthyroidism in the treatment group (group 1) and after a 6 month follow up in the observation group (group 2).

Method

Free T3 (FT3), free T4 (FT4) and ultrasensitive TSH were determined by microparticle enzyme immunoassay method (Axsym system, Abbott, IL) and intra-interassay CVs were 4.98%, 5.47%, 10.58% and 1.57%, 4.32%, 4.56%, respectively). Minimum concentration that can be detected by the TSH kit was 0.03 mU/l. Serum osteocalcin (Osteocalcina, Irmact, Roma, Italia) and SHBG (Immulite 2000, DPC, Los Angeles, CA) were measured by immunoradiometric assay (interassay CVs: 3.4%, 4.2% and intraassay CVs: 3.1%, 2.5%, respectively). Serum calcium, phosphorus, alkaline phosphatase, triglyceride, cholesterol, HDL, LDL, VLDL cholesterol and calcium and creatinine levels in a 24 hour urine sample were measured by an autoanalyzer. Bone mineral density was measured in L_{1-4} lumbar vertebra and femur neck by using dual energy X-ray absorbtiometry (Dexa, Hologic Inc., QDR-4500W, Waltham, MA). Ambulatory blood pressure was measured by attaching the device to the left arm. Digital Holter Recorder (St. Cours, Missouri) device was used in holter measurements.

Heart rate variability was determined by using time domain method. In a continuous ECG record, standard deviation of all NN intervals (SDNN), standard deviation of the averages of NN intervals in all five minute segments of the entire recording (SDANN),

the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), and mean of the standard deviations of all NN intervals for all five minute segments of the entire recording (SDNN5) parameters were used [7].

Statistical analysis

BMD of the patients and control group was compared by Mann Whitney U test and data on alcohol, cigarette smoking, exercise, milk-drinking habits were compared by Chi-square test. Before and after treatment/observation parameters of group 1 and 2 were compared by Wilcoxon test and correlation analysis was made by phi coefficient. Results were expressed as mean ± standard error. $P < 0.05$ was considered significant.

Results

Bone mineral density was decreased 1.3% in femur neck and 3.9% in vertebra when compared with the healthy controls. But there was no difference in BMDF and BMDL between two groups. Smoking, extra exercise and milk drinking properties of the two groups were similar, but mean FT4 and TSH levels were higher than the controls (Table 1). There was no alcohol drinker in either group. There was no difference between group 1 and 2 in the parameters compared in Table 2, but alkaline phosphatase was higher in the observation group.

The most common symptoms in group 1 were observed to be fatigue and nervousness (90%) followed by palpitation (70%) and over sweating (50%). Fatigue and palpitation regressed to 40% and over

Table 1. Comparison of clinical and biochemical parameters in the patient and control groups.

	Patients (n: 20)	Controls (n: 20)
Age (year)	36.10 ± 1.41	36.25 ± 1.50
Smokers*	8 (40%)	6 (30%)
Extra exercise habit*	5 (25%)	5 (25%)
Milk drinking habit*	13 (65%)	16 (80%)
FT3 (2.2-5.3 pmol/l)	4.06 ± 0.15	4.09 ± 0.12
FT4 (9.1-23.8 pmol/l)	14.10 ± 0.64**	13.67 ± 0.51**
TSH (0.49-4.67 mU/l)	0.22 ± 0.02**	1.01 ± 0.09**
BMDF (g/cm^2)	0.838 ± 0.020	0.849 ± 0.017
BMDL (g/cm^2)	0.979 ± 0.022	1.019 ± 0.016

Statistical analyses were made using Mann Whitney U test and *Chi-square test (**$p < 0.05$).

Table 2. Comparison of clinical and biochemical parameters in the group 1 and 2.

	Group 1 (n: 10)	Group 2 (n: 10)
Age (year)	38.70 ± 1.38	33.50 ± 2.24
Body mass index (kg/m^2)	25.90 ± 1.56	23.55 ± 0.91
FT3 (2.2-5.3 pmol/l)	4.37 ± 0.23	3.75 ± 0.15
FT4 (9.1-23.8 pmol/l)	16.38 ± 0.08	14.54 ± 0.64
TSH (0.49-4.67 mU/l)	0.23 ± 0.03	0.21 ± 0.03
Duration of SCH (month)	13.70 ± 3.42	18.00 ± 5.44
Calcium (2.1-2.5 mmol/l)	2.23 ± 0.03	2.24 ± 0.03
Phosphor (0.8-1.4 mmol/l)	1.01 ± 0.04	1.08 ± 0.05
Alkaline phosphatase (42-141 U/L)	52.10 ± 5.39*	73.80 ± 7.84*
Osteocalcin (male < 23.4, female: 1.6-7.4 ng/ml)	9.82 ± 3.35	7.33 ± 0.16
Urine calcium/creatinine (24 h) (5-175 μg/mg)	24.02 ± 8.00	15.11 ± 2.01

Statistical analyses were made using Mann Whitney U test (*$p < 0.05$).

sweating regressed to 10%; while tremor regressed to 0% from 10% after treatment. The most common symptom in group 2 was nervousness (70%) followed by heat intolerance (50%) and over sweating (30%). After 6 months, fatigue progressed to 60% from 40%, nervousness progressed to 90% from 70%, over sweating progressed to 40% from 30%, and heat intolerance showed a progression of 60% from 50%. While tachycardia regressed to 0% from 10% and tremor regressed to 10% from 20% (Table 3). We did not find any increase in confusion, myopathy, atrial fibrillation and deep tendon reflexes incidence in either group before and after treatment /observation period.

BMDL, BMDF, serum lipids and serum SHBG levels before and after treatment and before and after observation were compared in table 4. FT3, FT4, TSH concentrations of group 1 after treatment were 3.80 ± 0.17 pmol/l, 12.74 ± 1.40 pmol/l, 0.81 ± 0.24 mU/l, respectively. We found the mean FT4 concentration to decrease and the mean TSH concentration to increase significantly after treatment when compared with the before treatment values ($p< 0.01$). However, we could not find any statistically significant difference between pretreatment and posttreatment values of mean FT3 concentrations ($p>0.05$). There was no statistically significant difference between the groups in triglyceride, cholesterol, HDL, LDL, VLDL levels, but SHBG was decreased after treatment in group 1 ($p< 0.05$).

We did not find any significant difference between group 1 and group 2 in minimal heart rate, total number of ventricular and supraventricular ectopic beats, and SDNN, SDNN5, SDANN and RMSSD components of heart rate variability measurements (Table 4). While there was no supraventricular tachycardia run before treatment, in group 1 patients were observed to have it after treatment. Also we did not observe any supraventricular tachycardia run in group 2 before observation, but it developed in one patient at the 6^{th} month. Ventricular tachycardia run did not develop in any of the patients before and after treatment/observation period.

Daytime (between the hours 8.00–22.59) systolic and diastolic average blood pressure values together with night time (between the hours 23.00–07.59) average systolic and diastolic blood pressure measurements were compared before and after treatment /observation period in groups 1 and 2 on Table 4. Systolic blood pressure in group 1 was observed to decrease after treatment, in group 1. There was no significant difference in the before and after comparison of other parameters. While 5 patients were dipper before treatment and the total number of dipper patients became 7 after treatment in group 1, 7 patients were dipper before observation, and 6 of them remained dipper after the observation period in group 2.

Table 3. Symptoms and findings of the patients before and after treatment/observation*.

	Group 1		Group 2	
	Before therapy	After therapy	Before observation	After observation
Fatigue	90%	40%	40%	60%
Nervousness	90%	50%	70%	90%
Over sweating	50%	10%	30%	40%
Heat intolerance	40%	50%	50%	60%
Diarrhoea	10%	10%	0%	0%
Palpitation	70%	40%	30%	40%
Increased appetite	60%	20%	20%	20%
Decreased appetite	10%	30%	0%	10%
Lose weight	30%	30%	0%	0%
Tachycardia	10%	0%	10%	0%
Tremor	40%	0%	20%	10%

DTR: Deep tendon reflexes

*A scale involving hyperthyroidism symptoms and findings was derived from the studies of Davis and Trivelle was used (5, 6).

Table 4. Comparison of the results of ambulatory blood pressure, holter measurements, BMD and lipid levels in the patients before and after treatment/observation.

	Group 1		Group 2	
	Before therapy	After therapy	Before observation	After observation
BMDF (g/cm²)	0.828 ± 0.038	0.826 ± 0.042	0.848 ± 0.017	0.868 ± 0.019
BMDL (g/cm²)	0.991 ± 0.046	0.998 ± 0.048	0.968 ± 0.030	0.968 ± 0.031
Triglyceride (0.3–1.3 mmol/l)	1.40 ± 0.18	0.45 ± 0.27	1.06 ± 0.12	0.86 ± 0.16
Cholesterol (3.6–5.7 mmol/l)	4.74 ± 0.31	4.73 ± 0.23	4.19 ± 0.26	4.07 ± 0.17
LDL (2.1–4.9 mmol/l)	2.85 ± 0.23	2.74 ± 0.17	2.25 ± 0.18	2.36 ± 0.15
VLDL (0.2–1.3 mmol/l)	0.72 ± 0.09	0.75 ± 0.13	0.57 ± 0.08	0.44 ± 0.08
HDL (0.7–2.2 mmol/l)	1.41 ± 0.12	1.23 ± 0.10	1.36 ± 0.15	1.25 ± 0.09
SHBG (13–114 nmol/l)	69.19 ± 13.28*	48.30 ± 6.94*	82.78 ± 18.52	43.72 ± 5.14
Minimal heart rate (min)	48.90 ± 8.2	50.00 ± 1.93	48.80 ± 1.67	57.70 ± 2.51
Maximal heart rate (min)	138.10 ± 3.63	147.10 ± 5.53	148.30 ± 5.30	145.20 ± 6.86
Total ventricular ectopic beats	0	3.37 ± 3.0	0	0
Total supraventricular ectopic beats	5.75 ± 2.98	7.37 ± 4.53	3.40 ± 1.32	5.60 ± 2.06
SDNN (millisecond)	135.50 ± 9.25	128.70 ± 10.63	139.30 ± 10.61	128.00 ± 10.25
SDNN5 (millisecond)	59.90 ± 5.31	61.20 ± 3.66	68.00 ± 8.21	69.60 ± 10.79
SDANN (millisecond)	131.00 ± 9.52	117.60 ± 10.56	125.00 ± 9.71	122.80 ± 10.80
RMSSD (millisecond)	44.70 ± 6.25	44.10 ± 6.23	67.40 ± 16.06	52.30 ± 7.87
Mean SBP daytime (mmHg)	115.00 ± 2.78*	112.42 ± 2.66*	114.50 ± 3.21	113.70 ± 2.62
Mean DBP daytime (mmHg)	71.10 ± 2.37	69.40 ± 1.78	72.70 ± 2.00	72.10 ± 2.37
Mean DBP night time (mmHg)	62.80 ± 1.95	61.50 ± 1.40	62.30 ± 1.71	61.80 ± 2.80
Mean SBP night time (mmHg)	98.50 ± 2.96	100.10 ± 2.25	100.60 ± 2.29	101.60 ± 1.96

Statistical analyses were made by using Wilcoxon test (*$p < 0.05$).

A negative correlation was observed between TSH and osteocalcin ($r = -0.53$, $p < 0.05$) in the patients group before randomisation. While a negative correlation was found between FT3 and SDNN ($r = -0.43$, $p < 0.05$), SDANN ($r = -0.43$, $p > 0.05$), we observed a positive correlation between FT3 and the time for the attainment of euthyroidism ($phi = 1$, $p < 0.05$) and increased appetite ($phi = 0.49$, $p < 0.05$). There was a negative correlation between TSH and heat intolerance ($phi = -0.50$, $p < 0.05$). No other significant relation was found in correlation analysis for the other parameters.

Discussion

The most important matter in SCH is to determine whether it has organic findings and causes any effect on the general health, quality of life and life expectancy of an individual. It is not yet known if the treatment of SCH is rational or not [8]. In our study, the patients receiving antithyroid treatment were evaluated before and after treatment, and the patients who were observed without receiving any treatment were evaluated before and after observation for hyperthyroidism symptoms and findings. Fatigue, nervousness, over sweating, and palpitation has been shown to improve with treatment. Conversely in the observation group, the number of patients with fatigue, nervousness, over sweating and palpitation increased after observation. Helfand and Redfern found by screening that the patients with low TSH do not have more symptoms than their age and sex matched controls [9]. In a study comparing 31 patients with SCH and 27 normal subjects by their symptom, finding and psychometric tests, few differences were found between the groups [10].

Overt hyperthyroidism has been shown to decrease BMD and cause bone fractures [11, 12]. Different results from different studies investigating the changes in BMD prospectively have been obtained. Nielsen *et al.* found a 12% decrease in the forearm BMD while Linde and Friis found the BMD to be 28% decreased which later became normal by treat-

ment in patients with hyperthyroidism [13, 14]. Conversely Krolner *et al.* found 13% decrease in the BMD of lumbar vertebra and found this value to increase by only 3.7% after a one-year treatment [15].

The studies showing whether SCH has the same effects on bone and whether treatment is beneficial in the situation of osteoporosis are inconclusive. Two studies have shown that antithyroid treatment improves osteoporosis in patients with SCH, but the chosen patient group in both studies was postmenopausal women [16, 17]. The evident effect of menopause on BMD cannot be denied in these studies. Premenopausal women were included in our study in order to exclude the effect of menopause on bone in patients with SCH. In our patients, BMDF and BMDL were decreased 1.3% and 3.9%, respectively, when compared with the control group. But there was no difference between the groups in BMDF and BMDL. This result was consistent with other studies measuring BMD in other premenopausal patients with SCH. Földes *et al.* found that the lumbar vertebra, femur neck and radius BMD of patients with endogenous SCH did not decrease when compared with healthy controls [18]. Faber and Galloe made a metaanalysis study involving patients with SCH due to L-thyroxine treatment and did not find any decrease in bone mass during L-thyroxine treatment in premenopausal women [19]. Gürlek and Gedik compared the bone turnover metabolic parameters and femur neck, lumbar vertebra, forearm BMD measurements of 15 premenopausal patients with SCH with healthy controls, and did not find significant difference [20].

In our study, BMD was found to be unchanged in both the treatment-receiving group and in the observation group receiving no treatment after 6 months. In one study markers of bone resorption and formation were found to be still higher in overt hyperthyroidic patients 1 year after the attainment of euthyroidism. This indicates that bone remodelling is still going on at high velocity [21]. Termination of bone loss due to the normalization of serum TSH by antithyroid treatment is possibly related to the slowing of the remodelling process. Considering that the attainment of positive bone balance can take at least 2 years, the shortness of the treatment period could be a shortcoming of our study. But we can at least say that antithyroid treatment has no favourable effect on BMD after a 6 month period.

In the Framingham study, the age corrected incidence of atrial fibrillation after a 10-year observation was 28 per 100 subjects in patients with low serum TSH and 10 per 100 person for the subjects with normal serum TSH [22]. In our study, none of our patients had atrial fibrillation and it did not develop in the 6 month observation period in either the treatment or observation group. No significant difference was found in minimal heart rate, maximal heart rate, total number of supraventricular and ventricular ectopic beats between pre- and post-treatment values together with pre- and post-observation ones in either group. But it should be noted that our patient groups are young in age, the number of cases is small and our observation period is short.

The higher prevalence of hypertension can be found in patients with toxic adenoma probably due to its being more common in older patients. The reason for systolic hypertension in hyperthyroidic patients is thought to be the inability of the vascular system to accommodate the increase in stroke volume [23]. While the patients showing a nocturnal decrease in blood pressure is classified as dipper, the patients with no nocturnal decrease is defined as non-dipper in the literature [24]. Non-dipper status is related to an increase in cardiovascular complication risk [25]. None of our patients had hypertension problem in our study. Nevertheless we found a significant decrease of average systolic blood pressure between the time periods from 8 to 23 after treatment. While 5 patients were dipper before treatment and total number of dipper patients became 7 after treatment in group 1, 7 patients were dipper before observation and 6 of them remained dipper after observation in group 2. This may show that antithyroid treatment has a favourable effect in SCH patients in this context. But we think that this should be investigated in larger patient groups with longer observation periods.

Heart rate variability is a marker of autonomic activity and vagal activity is largely responsible for it. The decrease in heart rate variability shows that sympathetic tonus activity is increased while vagal tonus is decreased. A significant negative correlation was observed between FT3 and SDNN, which is a component of heart rate variability measurements. But we did not find any difference between pre treatment /observation values and post treatment/observation ones. The results of the studies made in patients

with hyperthyroidism are confusing. While Girard *et al.* [26] found in their study that due to the decrease of parasympathetic activity in patients with hyperthyroidism, the sympathetic part of the autonomous nervous system predominates, whereas Pitzalis *et al.* [27] found in their study that cardiac vagal activity is not disturbed in patients with hyperthyroidism.

Thyroid hormone affects SHBG synthesis and serum SHBG concentration indicates the effect of thyroid hormone at tissue level [28]. The decrease of SHBG by antithyroid drug treatment in our study could be accepted as the improvement of thyrotoxicosis at tissue level.

The lipid profile in patients with SCH is not clear. A decrease in serum total and LDL concentrations has been reported [2]. In a study made by an outpatient lipid clinic SCH was shown to change the lipid profiles of dyslipidemic patients and was observed to change even the effectiveness of hypolipidemic treatment [29]. In our study none of our patients had hyperlipidemia and lipid levels did not change by treatment.

In our study we observed that antithyroid treatment partially improves the quality of life, together with symptoms and findings. No favourable effect of 6 month treatment has been observed on BMD and cardiac parameters. These results show that the specific antithyroid treatment of patients with SCH diagnosed in a young age group is not useful and it would be better for them to be observed until overt hyperthyroidism develops. Our cardiovascular system related positive findings about treatment were the decrease in daytime average systolic blood pressure and the improvement of non-dipper status. But studies with longer observation periods are needed to investigate the extent to which these parameters affect mortality and morbidity in a general population.

References

1. Levy EG (2000) Subclinical hyperthyroidism. *Thyroid* 10: 721–723.
2. Marqusee E, Haden ST, Utiger RD (1998) Subclinical thyrotoxicosis. *Endocrinol Metab Clin North Am* 27: 37–49.
3. Hanna FWF, Lazarus JH, Scanlon MF (1999) Controversial aspects of thyroid disease. *Br Med J* 319: 894–899.
4. Greenspan SL, Greenspan FS (1999) The effects of thyroid hormone on skeletal integrity. *Ann Intern Med* 130: 750–758.
5. Davis PJ, Davis FB (1974) Hyperthyroidism in patients over the age of 60 years. Clinical features in 85 patients. *Medicine* (Baltimore) 53: 161–179.
6. Trivelle C, Doucet J, Chassagne P, Landrin I, Kadri N, Menard JF, Bercoff E (1996) Differences in the signs and the symptoms of hyperthyroidism in older and younger patients. *J Am Geriatric Sc* 44: 50–53.
7. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. (1996) *Circulation* 93: 1043–1065.
8. Cooper DS (1998) Subclinical thyroid disease: A clinician's perspective. *Ann Intern Med* 129: 135–138.
9. Helfand M, Redfern CC (1998) Screening for thyroid disease: an update. *Ann Intern Med* 129: 144–158.
10. Schlote B, Schaff L, Schmidt R, Pohl T, Vardarli I, Schieber H, Zober MA, Usadel KH (1992) Mental physical state in subclinical hyperthyroidism. Investigation in a normal working population. *Biol Psychiatry* 32: 48–56.
11. Fraser SA, Anderson JB, Smith DA, Wilson GM (1971) Osteoporosis and fractures following thyrotoxicosis. *Lancet i* 981–983.
12. Wakasugi M, Wakao R, Tawata M, Gan N, Koizumi K, Onaya T (1993) Bone mineral density in patients with hyperthyroidism measured by dual energy X-ray absorbtiometry. *Clin Endocrinol* 38: 283–286.
13. Nielsen HE, Mosekilde L, Charles P (1979) Bone mineral content in hyperthyroid patients after combined medical and surgical treatment. *Acta Radiol Oncol* 18: 122–128.
14. Linde J, Friis T (1979) Osteoporosis in hyperthyroidism estimated by photon absorbtiometry. *Acta Endocrinol* 91: 437–448.
15. Krolner B, Jorgensen JV, Nielsen SP (1983) Spinal bone mineral content in myxoedema and thyrotoxicosis. Effects of thyroid hormones and antithyroid treatment. *Clin Endocrinol* 18: 439–446.
16. Faber J, Jensen IW, Petersen L, Nygaard B, Hegedüs L, Nielsen S (1998) Normalization of serum thyrotropin by means of radioiodine treatment in subclinical hyperthyroidism: effect on bone loss in postmenopausal women. *Clin Endocrinol* 48: 285–290.
17. Mudde AH, Houben AJHM, Kruseman ACN (1994) Bone metabolism during anti-thyroid drug treatment of endogenous subclinical hyperthyroidism. *Clin*

Endocrinol 41: 421–424.
18. Foldes J, Tarjan G, Szatthmari M, Varga F, Krasznai I, Horvath C (1993) Bone mineral density in patients with endogenous subclinical hyperthyroidism: Is this thyroid status a risk factor of osteoporosis? *Clin Endocrinol* 39: 521–527.
19. Faber J, Galloe AM (1994) Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: A metaanalysis. *Eur J Endocrinol* 130: 350–356.
20. Gürlek A, Gedik O (1999) Effects of endogenous subclinical hyperthyroidism on bone metabolism and bone mineral density in premenopausal women. *Thyroid* 9: 539–543.
21. Pantazi P, Papapetrou PD (2000) Changes in parameters of bone and mineral metabolism during therapy for hyperthyroidism. *J Clin Endocrinol Metab* 85: 1099–1106.
22. Sawin CT, Galler A, Wolf PA, Belanger AJ, Baker E, Bacharach P, Wilson PWF, Benjamin EJ, D'Agoustino RB (1996) Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. *N Engl J Med* 331: 1249–1252.
23. Saito I, Saruta T (1994) Hypertension in thyroid disorders. *Endocrinol Metab Clin North Am* 23: 379–386.
24. White WB (2000) Ambulatory blood pressure monitoring: dippers compared with non dippers. *Blood Press Monit* 5: 17–23.
25. Manning G, Rushton L, Donelly R, Millar-Craig MW (2000) Variability of diurnal changes in ambulatory blood pressure and nocturnal dipping status in untreated hypertensive and normotensive subjects. *Am J Hypertens* 13: 1035–1038.
26. Girard A, Hugues FC, Le Jeunne C, Eleghozi JL (1998) Short term variability of blood pressure and heart rate in hyperthyroidism. *Clin Auton Res* 8: 181–186.
27. Pitzalis MV, Mastropasqua F, Massari F, Ciampolillo A, Passantino A, Ognissanti M, Mannarini A, Zanna D, Giorgino R, Rizzon P (1998) Assessment of cardiac vagal activity in patients with hyperthyroidism. *Int J Cardiol* 64: 145–151.
28. Nayer DE, Lambot P, Desmons MC, Rennotte B, Malvaux P, Beckers C (1986) Sex hormone-binding protein in hyperthyrotoxinemic patients: A discriminator for thyroid status in thyroid hormone resistance and dysalbuminemic hyperthyrotoxinemia. *J Clin Endocrinol Metab* 62: 1309–1312.
29. Tsimihodimos V, Bairaktari E, Tzallas C, Miltiadus G, Liberopoulos E, Elisaf M (1999) The incidence of thyroid function abnormalities in patients attending an outpatient lipid clinic. *Thyroid* 9: 365–368.